U.S. FOOD AND DRUG ADMINISTRATION

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PEDIATRIC ETHICS SUBCOMMITTEE

OF THE

PEDIATRIC ADVISORY COMMITTEE

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MEETING

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MONDAY,
JUNE 9, 2008

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The subcommittee convened at 8:30 a.m. at the Holiday Inn/Gaithersburg, Gaithersburg, Maryland, Norm Fost, Subcommittee Chair, presiding.

PRESENT:
NORMAN FOST, M.D., Chair
JEFFREY BOTKIN, M.D., M.P.H., Consultant
AMY CELENTO
ALAN FIX, M.D., M.S., Consultant
LEONARD GLANTZ, J.D., Consultant
STEVEN JOFFE, M.D., M.P.H., Consultant
ALEXANDER KON, M.D., Consultant
THERESA O'LONERGAN, M.A., Consultant
GEOFFREY ROSENTHAL, M.D., Ph.D.
ELAINE VINING
BENJAMIN WILFOND, M.D., Consultant

FDA PARTICIPANTS:
THERESE CVETKOVICH, M.D., Medical Officer, Office of Vaccines Research and Review, Center for Biologics Evaluation and Research
CARLOS PEÑA, Ph.D., M.S., Executive Secretary, PAC, Office of Science and Health Coordination, Office of the Commissioner
ROBERT "SKIP" NELSON, M.D., Ph.D., Pediatric Ethicist, Office of Pediatric Therapeutics, Office of the Commissioner
KAREN MIDTHUN, M.D., Deputy Director, Office of the Director, Center for Biologics Evaluation and Research
DIANNE MURPHY, M.D., Director, Office of Pediatric Therapeutics, Office of the Commissioner

PUBLIC SPEAKERS:
MICHELLE LALLY, Brown University
JEFF SAFRIT, Elizabeth Glaser Pediatric AIDS Foundation

T-A-B-L-E O-F C-O-N-T-E-N-T-S

P-R-O-C-E-E-D-I-N-G-S

8:35 a.m.

DR. BOTKIN: Good morning, everyone. We're going to go ahead and get started this morning.

I am Jeff Botkin from the University of Utah. I am not in fact Norm Fost. My privilege to get things kicked off this morning and to welcome all of you. And thanks to Carlos and Skip for their work in putting this committee together. And thanks to the FDA for funding and sponsoring this conversation today.

Norm is wending his way we understand from the airport here to the meeting. So hoping he'll be here within the hour or so. I think he was held up from weather through the Midwest as many folks have had difficulty across the country in this last day or two with some tough weather situations. So Norm will be joining us shortly.

Just a couple of brief comments

before we introduce ourselves, and then I turn it over to Carlos and Skip. This is a wonderful opportunity to talk about these issues.

As folks know, we're going to be concentrating on some of the more ethically complex aspects of this domain of research related to prospects of direct benefit. And I think as many of us have been thinking about research issues with kids over the years, there's been quite a bit of focus on many of the domains, many of the ethical complexities. But from my perspective -- and I think perhaps from Skip and the FDA's perspective -- relatively less concentration on this particular domain of research. Prospect of different benefit often times considered less ethically complicated than some of the other categories. But I think as the cases illustrate that have been prepared for our discussion, there's a lot of very interesting and complicated issues in this domain.

As I understand, our task over the next two days or so is to certainly look at these cases, but as stepping stones to a broader discussion of the issues relevant to these aspects. So the cases themselves are intrinsically important and I think reflective of the kinds of work that are going on out there. And so our thoughts about the cases will be important but perhaps more important to use the cases as a way of thinking about the broader issues in this domain.

So, thanks again to the FDA for the opportunity to think about this important and interesting area.

So perhaps the first part of our agenda, we should go around and at least our table here and hear a few sentences about who everybody is before we get started with the agenda.

Alan?

DR. FIX: Thanks. Alan Fix. I'm the branch chief of the Vaccine Clinical

Research Branch and the Vaccine Research Program at the Division of AIDS, NIH.

MR. GLANTZ: I'm Leonard Glantz. I'm on the faculty of the Boston University School of Public Health and the School of Law. And I'm a professor of health law and bioethics.

DR. JOFFE: I'm Steve Joffe. I'm a pediatric oncologist. I work at Children's Hospital and Dana-Farber Cancer Institute in Boston. And I'm the hospital ethicist at the Dana-Farber Institute.

DR. KON: I'm Alex Kon. I'm on faculty at the University of California/Davis. I'm a pediatric intensive care unit doctor and an associate professor of pediatrics and bioethics there.

MS. O'LONERGAN: I'm Terry O'Lonergan. I am a research bioethicist. And I'm at the Children's Hospital in Denver School of Medicine, Department of Pediatrics.

DR. WILFOND: I'm Ben Wilfond from

the University of Washington. I'm a pediatric pulmonologist by training. And I'm the director of the Treuman Katz Center for Pediatric Bioethics at Seattle Children's Hospital.

DR. BOTKIN: And I'm Jeff Botkin, general pediatrician, bioethics, at the University of Utah. And I'm associate vice president for research integrity.

DR. PEÑA: Carlos Peña, executive secretary to the Pediatric Ethics Subcommittee.

DR. ROSENTHAL: My name is Jeff Rosenthal. I'm a pediatric cardiologist at the Cleveland Clinic, and I'm a member of the Pediatric Advisory Committee as well.

MS. VINING: Hi. I'm Elaine Vining. I am the consumer rep for the Pediatric Advisory Committee.

MS. CELENTO: Amy Celento, patient rep to the Pediatric Advisory Committee.

DR. NELSON: And I'm Skip Nelson.

I think my nickname is Skip Robert, the official name for those who don't know, but I assume Skip will end up being tossed around a lot during the meeting. But I'm the pediatric ethicist with the Office of Pediatric Therapeutics in the Office of the Commissioner at the FDA.

DR. CVETKOVICH: Theresa Cvetkovich. I'm a medical officer in the Division of Vaccines in CBER.

DR. PEÑA: Good morning to the members of the Pediatric Ethics Subcommittee, members of the public, and FDA staff. Welcome to this meeting.

The following announcement addresses the issue of conflict of interest with respect to this meeting and is made part of the public record to preclude even the appearance of such at the meeting.

Today, Monday, June 9th, the Pediatric Ethics Subcommittee of the Pediatric Advisory Committee will meet to discuss the

application of 21 CFR 50.52 to FDA regulated research. The discussion will be illustrated with hypothetical case examples of research involving HIV vaccines and a lessons and control trials of inhaled corticosteriods in children with asthma.

On Tuesday, June 10th, the Subcommittee will meet to discussion the application of 21 CFR to FDA regulated research illustrated with a hypothetical case example of research using stem cells for treating periventricular white matter injury in children.

Based on the submitted agenda for the meeting and all financial interests reported by the Subcommittee participants, it has been determined that all interests in firms regulated by the Food and Drug Administration present no potential for an appearance of a conflict of interest at this meeting. In general, the Subcommittee participants are aware of the need to exclude

themselves from involvement in discussions of topics if their interest would be affected. And their exclusion will be noted for the record.

With respect to all other participants, we ask in the interest of fairness that they address any current or previous financial involvement with any firm relevant to a topic on the agenda or whose product they may wish to comment upon.

We would like to note that Ms. Amy Celento is participating as a pediatric health care representative, and Ms. Elaine Vining is participating as a consumer representative on this Subcommittee. Both Ms. Celento and Ms. Vining and Dr. Rosenthal are also all members of the parent advisory committee.

We have two open public comment periods schedule -- one today at approximately 1:00 p.m., and the second scheduled for tomorrow at approximately 8:00 a.m.

I would just remind to turn on your

microphones when you speak so that the transcriber can pick up everything that you state, and turn them off when you're not speaking. I also request all meeting attendees to turn their cell phones and blackberries to silent mode. Thank you.

DR. BOTKIN: Skip, I believe you're up.

DR. NELSON: Good morning. I'm going to start the meeting with three short presentations. And I appreciate these screens are small, but I'm assuming people that side can look at this one, people this side at this one, and you all in the audience, we put up another one so you could actually see the slides as well.

The first presentation is going to be a brief meeting agenda overview. And then I'll give a background on Subpart D. And then we'll get into the case presentations and slides as well. So hopefully all our technology will work just fine.

So I want to start off by reminding people about the charter of the Pediatric Advisory Committee, and in particular the role of the Pediatric Ethics Subcommittee, because in fact it is unique among FDA advisory committees.

The charter of the Pediatric Advisory Committee states that "it advises and makes recommendations to the FDA Commissioner regarding the ethics, design and analysis of clinical trials related to pediatric therapeutics and research involving children of subjects under 21 CFR 50.54, and to the HHS Secretary under 45 CFR 46.407" -- it's not important for this meeting to know what 50.54 refers to, but I'll at least mention that the role of the permanent Pediatric Ethics Subcommittee is to advise and make recommendations to the Pediatric Advisory Committee. Part of the reason for that language is subcommittees cannot advise the Commissioner directly. That's why that exists

-- "on pediatric ethical issues, and IRB referrals related to clinical investigations involving children of subjects under 21 CFR 50.54 and 45 CFR 46.407."

Now those two regulations are the ones that govern IRB referrals to the federal government for review. This is the fourth meeting of the Pediatric Ethics Subcommittee. All three previous meetings have been specifically on IRB referrals. So this is the first meeting where there's been a general discussion of ethical issues involving pediatric research.

And then the charter goes on to state that "the Pediatric Ethics Subcommittee will consist of two or more members of the Pediatric Advisory Committee" -- and we have three members here -- "and additional experts in science, medicine, education, ethics and law" -- of which the remainder of you all -- "to address specific issues within their respective areas of expertise." That's

basically what brought this committee into existence.

Now the overall focus of this meeting is to discuss the application of 21 CFR 50.52. I'll go into that in more detail for those who are not familiar with it, but this is the section of Subpart D that involves clinical investigations where there is greater than minimal risk, but that present the prospect of direct benefit to individual subjects. And the idea is the application of this to FDA-regulated research.

Today in the morning, we'll be talking about a hypothetical case using an example of research involving HIV vaccines in adolescents. This afternoon, we'll be talking about a hypothetical case of a controlled trial of inhaled corticosteroids in children with asthma. And then tomorrow morning -- June 10th -- we'll talk about a hypothetical case of research using stem cells for treating neonatal hypoxic-ischemic injury. And that's

basically the broad outline.

Now the structure of the discussion as you'll see is fairly straight forward for each hypothetical case. There will be a presentation prior to the case of selected ethical concepts that may be pertinent to the case discussion. They'll be a presentation of the hypothetical case description and the discussion questions, and then discussion. And that'll be pretty much our format for this morning, this afternoon and then tomorrow morning.

As Carlos mentioned, they'll be time for an open public hearing each day -- 1:00 o'clock today, and then I believe 8:00 a.m. tomorrow morning.

And the important issue as Jeff mentioned is for a general discussion also of this prospect of direct benefit greater than minimum risk category at the end of the three case discussions. But also hopefully as each case stimulates a discussion of these issues,

one could begin to draw out some sort of general observations around this.

And the idea is to not remain -- if you will -- tied to the case. But as Norm would probably say, now or after he arrives, you can't do good ethics without good facts. You need a case to sort of get the discussion going.

I think this would be somewhat of a rather boring and dry discussion if we said talk about prospects of direct benefit. Go. And to see what happens. That would be very difficult. So the purpose of the cases is to get us going, but hopefully not to be where we end.

So that's basically the presentation. Again to re-emphasize it, these are hypothetical cases, but real issues. And hopefully, I'm looking forward to this discussion.

There are probably no questions. You can ask about that. But I'm happy if

there are any to address them, Jeff, at this point.

DR. BOTKIN: Good. I think that'd be a nice opportunity if any of the committee members have any general questions about our agenda for the next two days.

DR. NELSON: Okay. Well, I thought it would be helpful to give a sort of general overview of 21 CFR 50, Subpart D. Many of the people around the table, many of the people in the audience may be familiar with these. But I thought as a way of laying out -- if you will -- the terrain and showing people where the particular category we'll be discussing fits, that it would be worth having that general presentation.

And as I think about the protections for research involving children, I've started to use the metaphor of nested protections. And as you'll notice in the tree -- the basic starting point of pediatric protections -- is that there's the scientific

necessity of using children in the research. And I'll talk a little bit more about that. Then the nest is the appropriate balance of risk and benefit. And a lot of our discussion today -- in fact all of our discussion -- will be around how one assesses that under prospect of direct benefit.

And then once you've decided there's an appropriate balance of risk and benefit, the next aspect is parental permission. That's the parent blue jays there feeding their young. And then you have child assent. Now certainly you all could discuss it, but we're basically focusing pretty much on the appropriate balance of risk and benefit and not really on issues of parent permission and child assent, at least as our direct focus.

So let me talk a little bit about the principle of scientific necessity. As I see this, it's driven from the notion of minimizing risks and equitable selection. And

a way of stating it is that children should not be enrolled in a clinical investigation unless it's absolutely necessary to answer an important scientific question about the health and welfare of children. And some of the ways this is worked out in the context of a protocol is that the study design should be capable of answering a question -- fairly straight forward -- sample size, control group, blinding, et cetera.

One of the practical applications of this in FDA-regulated research is called extrapolation. And I will get into that in a little bit more detail. But the overall objective is to achieve a public health benefit for children.

Now the general regulations -- 21 CFR 56 -- have two criteria for IRB approval of research that I at least would link this principle of scientific necessity to. The first is the notion of minimizing risks. You would eliminate any research procedure as

unnecessary that does not contribute to the scientific objective. It's important that this is a research procedure. As Steve for example knows, often in oncology there's a lot of clinical procedures that are bundled with a research protocol. I'm not talking about eliminating procedures not pertinent to the scientific objective, but eliminating research procedures that do not contribute to that scientific objective.

The second is equitable selection. We often think about that in the context of gender and racial equity. But the way it was originally developed if you look back at the National Commission was to talk about the notion of subjects who were capable of informed consent -- in other words, adults -- being enrolled prior to children. And you should not enroll children unless essential, in other words there being no other option whether animal or adult human.

Now in the past, this has resulted

in the exclusion of children. But we now appreciate that it's important to include children in research when we in fact need that information to direct appropriate therapeutics.

Now to give you an illustration of this principle from our friends across the Atlantic, the European Medicinal Agency has a guidance that they published in 2008 -- I believe in January -- where they state that children should not be included in clinical trials when the research can be done in adults capable of informed consent. Proof of concept should first be obtained in relevant animal models or in adults whenever possible. I added that emphasis. The point is if it can't be done, it can't be done but whenever possible. In one of our cases, that will be one of the issues we'll discuss primarily tomorrow morning.

If research with children is necessary, the least vulnerable are usually

included -- older rather than younger -- and that the pediatric population is based on the target population for the tested medicine, the possibility of extrapolation, and then the scientific validity of that approach. The Declaration of Helsinki also includes this particular principle -- paragraph 24 -- which is not the paragraphs that are usually being discussed, but points out that these groups -- one of which is legally incompetent minors -- should not be included in research unless -- emphasis added -- the research is necessary to promote the health of the population represented, and that the research cannot instead be performed on legally competent persons. So this is also what I would call the principle of scientific necessity within that Declaration.

So let's talk a little bit about extrapolation because this is something that's been developed within FDA and is actually included in the regulations authorizing

pediatric research. It's in the Pediatric Research Equity Act of 2007. But it dates back into the mid-1990s when the stimulation of research in pediatrics was started.

The notion is if the course of the disease and the effects of the drug are sufficiently similar in adults and pediatric patients, the Secretary -- which is another way of saying that the FDA then advising the Commissioner advising the Secretary -- may conclude that pediatric effectiveness can be extrapolated from adequate and well controlled studies in adults, usually supplemented with other information obtained in pediatric patients, such as PK studies. So the idea here is if it's the same disease and the same response -- again the scientific question that would need to be answered -- one may not do efficacy studies as opposed to simply dosing and safety studies.

This principle has been developed into an algorithm, which basically asks these

questions in sequential order. Is it reasonable to assume that the child has a similar disease progression? If the answer's no, you basically have to do all of the studies -- efficacy, safety, dosing. If the answer's yes, then is the response the same? If the answer's no, you've got to do all the studies. If the answer to that is yes, is it reasonable to assume that there's an appropriate concentration response? If the answer is yes, then maybe you just need to do dosing and safety. If the answer's no, can you find a biomarker? If the answer's no, well then you're back to square one. If you can't find a biomarker, then you may have to do all of the studies. If you can, you may simply have to concentration response.

This algorithm was published in 2003 in an FDA guidance on exposure response relationships. But it is the algorithm that informs FDA when it's deciding what studies to basically either request -- underwritten

requests -- or require under PREA.

Now note that the selection of the appropriate dose and the assessment of safety is never extrapolated. And that basically the extrapolation of efficacy requires some understanding of disease pathophysiology and mechanisms of therapeutic response to the investigational product. So for example, you may do some bridging studies that could be required to support extrapolation such as a humoral or cellular immune response. So that's basically extrapolation.

Now let me run through briefly the appropriate balance of risk and benefit. And this is to set into context the particular regulation we'll be talking about at this meeting.

One way of understanding the additional protections for children is to put it in the context of the adult regulations. And if you look at 21 CFR 56.111, there for doing research involving adults we can balance

the reasonableness of the risks in relationship to anticipated benefits -- if any -- and the importance of the knowledge. If you look at the logic of that, that basically means we can ask an adult to go into risky research if the knowledge is worth getting. They don't necessarily have to have direct benefit.

If you look at research involving children, if there is in fact no prospect of direct benefit, the research risk is restricted to either minimal risk or a minor increase over minimal risk. Or if you look at the ICH E6 Good Clinical Practice Guidelines, the word there low.

On the other hand, for research offering prospect of direct benefit, the justification of that risk exposure is further constrained. And that's the particular regulation that we'll be talking about in this meeting.

Now just to run through the

relationship, if you look at direct benefit or no direct benefit, minimal risk, greater than minimal risk, you end up with three categories. And to give you briefly a run through, the first category would be research presenting minimal risk. This is the definition of minimal risk. It has been the subject of much discussion within the literature and within national commissions where it basically defines minimal risk as the probability and magnitude of harm or discomfort anticipating the research are not greater in and of themselves than those ordinarily encountered in daily life or during the performance of routine physical or psychological examinations or tests.

That was a very quick cab ride, Norm. Welcome. Feel free to come up and take your chair at the front. This is Norm Fost who just arrived. We can allow you to introduce yourself a little later.

So that's minimal risk.

Now the next category is this minor increase where it talks about again research that does not offer prospect of direct benefit could present only a minor or slight increase. It talks about commensurate experience, and then disorder or condition. That's the other category.

The third category -- and this is the one that the cases that we're going to be using to stimulate discussion -- is the focus of this particular meeting. And the criteria for approval of that kind of research is it talks about the risk of being justified by the anticipated direct benefit to subjects within each arm of the study, and that the relationship of anticipated direct benefit to risk is at least as favorable as available alternative approaches.

So one could view the sort of discussion of the application of these -- if you will -- general guidelines and principles to FDA-regulated research as precisely the area we'll

be exploring over the next day and a half using our three hypothetical cases to stimulate discussion. So the focus of our meeting is on this particular regulation, again, clinical investigations involving greater than minimal risk but presenting the prospect of direct benefit to individual subjects.

This is the complete language of the regulations, so people have that in mind. If you're not familiar with it, any clinical investigation in which more than minimal risk to children is presented by an intervention or procedure that holds out the prospect of direct benefit for the individual subject, or by a monitoring procedure that is likely to contribute to the subject's well being may involve children subjects only if the risk is justified by the anticipated benefit to the subjects, the relation of the anticipated benefit to the risk is at least as favorable to the subjects as that presented by available

alternative approaches, and then adequate provisions for assent of the children and permission of the parents as set forth in the regulations under 50.55.

So that is the focus of the meeting. But I wanted to set that regulation into the broader context so that those who aren't familiar with the regulations see that we're really pretty much taking a specific subset -- if you will -- of pediatric research and exploring the ethical issues that arise in the application of that regulation to FDA-regulated research using our hypothetical cases.

So I'll stop and pause there as well, Jeff, to see if there's any questions. Perhaps we can even let Norm introduce himself, and before we get into the actual first case.

DR. FOST: Thank you, Skip. Sorry to be late, and glad to be here.

I'm Norm Fost. I'm a general

pediatrician at the University of Wisconsin School of Medicine and Public Health with an interest in child abuse, and Director of the Bioethics Program there since 1973. Also chair of the IRB for 31 years, which I'm hoping will get me into the Guinness Book of Records. And I've been a human subject, and I've been an investigator on large clinical trials, so I have some experience in that background also.

Thanks again.

DR. NELSON: I'll open to any questions, although I'm not sure there would be at this point. But any comments or questions from the Committee at least about the introduction before we launch into our first case.

DR. JOFFE: Actually Skip, I will as a question. And maybe I should ask this after the previous presentation.

But the question is the information and insights in discussion from today's and

tomorrow's meeting, what do you envision you and the FDA doing with that information? How do you plan to take that forward?

DR. NELSON: Well, at this point I guess the most I would say is I have a personal goal to start developing guidance around the application of Subpart D to FDA-regulated research. Having said that, there is not draft. There's no words on paper. So this is a very early first step in that process.

I think the second point as Jeff had mentioned, much of the discussion of Subpart D over the last decade -- if you will -- by the national advisory committee, by the Institute of Medicine and by the Secretary's Advisory Committee have focused largely on other aspects of Subpart D and not this particular area. And in many ways, I wanted to get this discussion going to try and address what I see as a gap to date, not in the regulations themselves, but in the

discussion of the issues around those application, particularly to inform the next step. So that's my personal goal.

But I say that only because to say there's guidance and development is a much different issue than saying I would like to start that process. That's where we are.

DR. FOST: Questions or comments about -- should we move into the case?

DR. NELSON: You're the boss.

So you all should have a written description of these cases. I might say that all of the information that's being presented is on the FDA website under the Advisory Committee. For those who are looking for it, what you won't see is the articles that we're not allowed to post because of copyright restrictions. But all of it is available in the public domain and the like.

So the first case, I'm just going to present that to get us moving.

It's important to recognize that

the following case description uses published information to construct a generic description of a typical clinical investigation that is not unique or specific to any particular product.

So the proposed clinical trial is a phase 2 proof of concept trial of a new vaccination strategy against HIV infection is being considered. The infection is being considered. The strategy combines three initial priming vaccinations with a DNA vaccine that incorporates selected HIV genes including envelope, following at six months by a modified poxvirus vectored vaccine containing the same HIV genes.

Pre-clinical testing of this prime boost regimen demonstrated relative protection against homologous simian immunodeficiency virus challenges in nonhuman primate models involving mucosal exposure. Although the vaccine did not prevent HIV infection, immunized animals had a reduced per exposure

probability of becoming infected as compared with controls.

Several phase 1 clinical trials involving health adult volunteers demonstrated T-cell responses lasting in the majority of subjects out to 12 months. In these adult studies, no serious adverse events were identified. The most common local reactions were pain and erythema at the injection site experienced by the majority of subjects. Mild and moderate fatigue and myalgia lasting up to four days occurred in a minority of subjects.

Of note, the majority of subjects also developed false-positive results from commercial HIV screening tests at the dose selected for phase 2 testing. Additional testing can discern false versus true positive tests for HIV infection. However, the duration that commercial screening tests for HIV remain positive is unknown. To date, there is no immunological surrogate that can serve as a short-term marker for potential

clinical benefit in reducing the incidence or mitigating the severity of HIV infection.

The phase 2 clinical trial plans to enroll a sufficient number of high-risk adult subjects 18 to 30 years of age to be able to evaluate first whether the vaccination regimen reduces the acquisition of HIV infection as the primary endpoint, and/or decreases the viral load at three months post-diagnosis in those subjects who become HIV infected.

The study will be conducted at multiple sites selected based on a high prevalence of HIV infection. After informed consent, subjects will be randomized equally to either active or placebo vaccination administered in a blinded fashion to minimize bias.

The study duration has been estimated based on a sufficient number of HIV infections occurring in the enrolled subjects to assess the primary endpoint. Risk reduction counseling, use of post-exposure

prophylaxis and standard anti-retroviral treatments for those subjects who become HIV infected during the trial are all included in the protocol. Interim analyses are planned for safety and efficacy after half of the necessary HIV-infected cases have occurred.

The question that will hopefully stimulate discussion, please discuss the ethical considerations that should go into a decision about whether -- and if you ask when -- to enroll adolescents in the above phase 2 clinical investigation. As part of your discussion, please address the threshold of evidence necessary to establish that the study intervention offers a sufficient prospect of direct benefit to justify the risks of vaccine administration.

For example, are interim or final results from adult phase 2 or 3 studies needed prior to studies in adolescents? How does the lack of an immunological surrogate for clinically meaningful benefit affect the

prospect of direct benefit? Issues you yes include the distinction between evidence sufficient to establish the prospect of direct benefit versus evidence sufficient to establish efficacy, the choice of adolescent populations, i.e., at risk, and the use of comparable adolescent immunogenicity and/or safety data as a bridge to extrapolate from adult clinical outcomes data to efficacy in the adolescent population.

I might say we do have content experts available to the committee. The main intent there is to not get you hung up on the technical aspects, but allow you to focus on the ethical issues and if questions then about the sort of -- if the technical questions and the science arise, we can at least address them in order to allow you to then move forward into the ethics.

So with that, I'll sit down and turn it over to Norm.

DR. FOST: Thank you. I just want

to respond to Steve Joffe's question to state my understanding of what we're supposed to accomplish today based on conversations with Skip before the meeting.

There are no actions items here today, so we're not being asked to make the recommendation. There will probably not be votes on anything. It's really the luxury of an open discussion. Hopefully it will be somewhat structured. I'll try to keep it on task. But anything and everything that's relevant to the issues that are outlined or even raised by these cases are up for discussion.

And the goal is that it will be a successful meeting. And my understanding is that Skip and the Agency's goal is that it will be a successful meeting if this is a robust and rich discussion. They have more insight into how to apply Subpart D on cases or trials of the sort that we're raising.

So, we should be uninhibited. And

I'm going to open by just suggesting we just not go around the table formally but allow people to just respond to general comments about this case or about this proposed trial. If you need a little focus for that, maybe the general question Skip listed is whether a trial like this needs to be done in adolescents at all at this stage of the proceedings of where this vaccine is.

So with that as background, I'll recede into the background, and hope somebody will start the discussion by saying whether they think there's any need to include adolescents in this stage of this new entity at all.

MR. GLANTZ: I guess the question I have about the case is why this isn't the perfect case for extrapolation. And it depends on what we mean by adolescence. But that if you're talking about 16- and 17-year-olds, is there any reason to believe that an 18-year-old and a 17-year-old would react

differently, either in terms of the risk or the benefit of this, or even a 16-year-old.

So what's interesting about the literature in reading about this is that it has adopted sort of legal standards for adolescence, which is 18, and which is entirely arbitrary of course, as opposed to based on any kind of biological or physiological reality.

So I guess in a sense what I'm asking is why not just give the 15- or the 16- and 17-year-old sort of a free ride, that is the research that's done on the adults that we could clearly extrapolate -- let me put that out -- to the 16- and 17-year-olds, and therefore no research ever needs to be done on that population for this purpose.

DR. FOST: Responses to Len's challenge?

Well, I can think of one. The readings discussed behavioral differences of adolescents. It may not be reasonable to

expect any great biologic difference between a 16-year-old and a 19-year-old. But behaviorally, disinhibition, for example, was described might entering an adolescent into this trial give him or her the false impression that he's or she's been protected and lead to more risk taking than what otherwise would occur, and if the vaccine's not effective, therefore, more risk. So either behavioral differences that wold warrant including adolescents even in the 15- to 18 group.

MR. GLANTZ: Yes. I just wonder if there's any data to support that, or if that is sort of our adolescent bias. Particularly, I don't see 18-year-olds or 19-year-olds being more disinhibited or less disinhibited than a 17- or a 16-year-old.

DR. FOST: I think the proposal here was whether or not to include 15- to 18-year-olds. So is 15 different from 19? Ben?

DR. WILFOND: Before I answer that

question, I want you to clarify something, Norm. I thought that behavioral disinhibition as it relates to the research study would be a justification for not including them, because presumably you'd want to wait until you really knew this thing really worked before you accept that risk. So you're actually agreeing with Len about not using that group for that reason?

DR. FOST: Right. I just meant to say there may not be a biologic difference, but there may be behavioral differences that would lead in that direction.

DR. FIX: I may have misunderstood the point, but perhaps one of the points is extrapolation from a study that does not include 16- and 17-year-olds when it comes to licensure.

MR. GLANTZ: Right. It'd be what you know about it.

DR. FOST: Jeff?

DR. BOTKIN: A related point I

guess, and one would be a question about how the adult study would be done and whether in fact you'd have enough individuals within that adult cohort that were on the younger end of that spectrum to give you data that you could extrapolate. In other words, if the mean age of the adult population was in their 30s and you had a relatively small number of individuals who are sort of in the 18 to 22 range, would you really have information that would be adequately extrapolatable from the adult cohort into the pediatric?

And I guess one of the other issues which sort of comes from a general sense that you don't know until you know and that there's oftentimes issues that you don't anticipate that then arise. And one of the interesting things about the background reading was the fact that some of these vaccine trials have demonstrated increased susceptibility, potentially the HIV, based on prior exposure with an experimental vaccine. So I guess to

me that would raise the question of whether adolescents by virtue of past history of infectious experience in the world might for reasons that we can't currently anticipate turn out to be quite a bit different than adults related to a vaccine trial.

So I guess I'd be just generally hesitant about the adequacy of an extrapolation approach in this context.

DR. FOST: Skip?

DR. NELSON: Just a procedural reminder. We are transcribing this. So as people make comments, if Norm hasn't introduced you by name for the benefit of the transcriptionist, say your name because it'll be the best way we can then go back and sort of follow the discussion. I know the passion may prevent that. But be nice.

DR. FOST: Other comments on this issue?

DR. JOFFE: Steve Joffe. Jeff makes a general point about not sort of a

presumption against extrapolating from young adults to older adolescents for example. But I wonder if there are other sort of scientific considerations on the table that would argue for not extrapolating from the 18- to 22-year-olds, say to the older adolescent and for actually doing the studies. Because as you started your discussion in this area, Skip, scientific necessity was the first point you raised. And so I think the first thing to sort of clarify here is what's the argument that there is scientific necessity at least to including older adolescents? I assume we'll be talking about younger adolescents later on.

DR. FOST: Ben? Go ahead.

DR. WILFOND: Actually, Steve's point made me think about something I've been thinking about which has to do with the distinction between scientific necessity and convenience or feasibility.

It seems to me that often one of the biggest challenges in any clinical trial

is recruitment. And I imagine there can be two very different scenarios in which scientific necessity would play itself out.

One is in which we thought it was highly easy to recruit adults for the study. But the message would be to say we can't do it in adults. We have to take more time to figure out how to do this in adolescents even though it'll take us more time to find those adolescents.

On the other hand, maybe the circumstance is well, it's actually kind of hard to find the adults. So one of the reasons for trying to broaden and include adolescents is that will actually make recruitment more feasible and easier to do. And I imagine that we might look at those issues differently in those two circumstances.

DR. FIX: Alan Fix. I just wanted to throw one additional issue that's tied in with the scientific necessity. And I don't think it's completely distinct. And that's

the regulatory necessity in moving towards making available whatever's eventually licensed available to adolescents when it's initially licensed. And for that's a huge issue. Obviously it's got to be done responsibly and taking into consideration all of these aspects including the behavioral issues.

I think one of the issues here though is that clearly this study is not a study that's intended to lead to licensure. And so there's a question of timing as to when to introduce the necessary investigation in the adolescents in that path to licensure.

DR. FOST: Could I raise a question about that? Most pediatric drugs are prescribed off-label -- 80 percent by actual FDA numbers. Are vaccines different in that regard that is if it's licensed for 19-year-olds and above, is there some limitation on giving to an 18-year-old or a 17-year-old? Is it more difficult to do that for vaccines than

for other traditional pharmaceuticals?

DR. CVETKOVICH: Therese Cvetkovich from CBER. I'd say in general for vaccines there's much less off-label use. I get the point about administration to an 18-year-old versus a 19-year-old which is not a distinction. But in terms of labeling, I think pediatrician would probably pretty much stick to the label unless there were evidence otherwise.

DR. FIX: Another huge issue here is issues of policy and application. And so certainly off-label use would be an individual consideration of a practitioner. But if you're looking for introduction of such a necessary intervention, population basis, relying on off-label use becomes problematic.

DR. BOTKIN: So let me clarify the issue then from a regulatory standpoint is it correct to say in order to be licensed for that age group that it must be tested, there must be data within that age group? Can you

extrapolate from a regulatory perspective? Or is the question we're asking here then when is it that adolescents ought to be incorporated in these studies? Off the bat along with other adults as folks are recruited? Or as Skip outlined, should there be a fairly robust data set out of adults before we would think about initiating research with adolescents?

DR. CVETKOVICH: Therese Cvetkovich. I just want to clarify the regulatory aspect. We can extrapolate efficacy clearly. That's in our regulations. There's no question about it. And we have done so for instance in the HIV field for anti-retrovirals. That was the absolute mechanism by which all the anti-retroviral drugs for kids got out there. So there was efficacy in adults supported by PK and safety in children.

In this instance, it's a little harder to say right off the bat, oh yes, we can extrapolate. We just don't know enough.

So it's a little bit difficult.

If we had a vaccine that prevented every infection right off the bat, and it appeared wonderfully safe, et cetera, et cetera, that would definitely be on the table, which is not to say that we might not want additional data to support use in the younger age group. But considering postpubertals who are distinct because of the legal consent issues, physiologically and there may be other issues that needed to be studied. But in general, the efficacy could be could be extrapolated. Whether we're there yet, I don't know.

MS. O'LONERGAN: One --

DR. FOST: State your name.

MS. O'LONERGAN: Terry O'Lonergan.

Alan raised the issue of policy, which I think is something to consider as far as when we're enrolling adolescents or not. It depends if your insurance company will cover the vaccine, and if your insurance

companies won't cover it if it's not labeled for use in pediatrics.

So if you intend to use it in children 15 to 18, if it's not labeled for that use, then effectively it's not going to be used by pediatricians because if insurance companies don't pay for it -- and one instance would be the shingles vaccine in older adults. If you're a year under what FDA has recommended for use, your insurance company won't pay for it. And it's quite expensive. And I would imagine that this would be the case as well.

So policy really does need to come in I think to the considerations.

DR. FOST: Is this a vaccine that if it hits a home run and becomes safe and effective is going to be used in insured populations? What's the target population? I would assume that in the early stages of such vaccines, both the studies and the use would be in extremely high-risk populations.

MS. O'LONERGAN: Certainly. I think it would be in high-risk populations, but we know that HIV extends beyond high-risk populations as well. So if we're talking about children who have routine blood transfusions and things like that that perhaps it would extend beyond the high-risk population.

DR. FOST: But I would assume -- I'm just making an ethical statement, not a regulatory one -- you wouldn't give a vaccine to a population in which the risk of HIV was one in a million. If the vaccine had any adverse effects at all, it would be worse if they had serious adverse effects. So in the beginning at least, HIV vaccines I assume would be mostly used in populations that by and large are not insured.

DR. FIX: Alan Fix. I'll have to keep saying my name, I guess.

I think the flip side to that is if it's not approved for that population -- that

age group -- how do the high-risk populations get access to a vaccine?

DR. FOST: Well, presumably from public health programs, not necessarily through private insurance.

DR. KON: Alex Kon. So I think that that's a very interesting question -- this whole question of who's the target population.

If we look at the HPV vaccine, I think that that was a big part of the conversation for that was that the original concept was you're going to be targeting how-risk. And now we're really talking about -- particularly the drug industry -- targeting every female in the country. And I think a lot of people have bought into that for good and bad reasons.

But I think if we're talking about an HIV vaccine, certainly at first we'd be talking about high-risk populations. But if the positives heavily outweigh the negatives,

I think very quickly we'd be moving to mass vaccination. Potentially it would be just be part of the routine vaccinations of pre-kindergarten, just to hit everybody. It's not that hard to imagine. So I think it becomes important when we're thinking about that.

DR. FOST: You mean whether it was a good idea or not, that's what would happen?

Could I just go back to Jeff's comment about you don't know until you know? How fine do you want to tune that? Again, this is an ethical question, not a regulatory one.

So children come in all shapes and sizes from zero to 18. But we don't think a 16, one-month person is different from a 16, two-month person. So do we think a 16-year-old is significantly different from a 17-year-old that we have to make sure that the study population has equal numbers or sufficient numbers of 16-year-olds and 17-year-olds? I presume not.

So what's special about 15 to 18? Or if you have a large cohort of 18-year-olds, do you really think it's an important scientific question? Well, we really don't know whether 17 1/2-year-olds. So where can we start to be a little bit more practical about these guidelines and not insist that we have to study every drug or every vaccine in every single increment of age group. What's a big enough lumping? Why isn't 15 to 18 -- or to go back to Len's original point -- why isn't 16 comparable enough to 18?

DR. BOTKIN: This is Jeff. I guess there's a couple thoughts. Certainly to begin with, who's the at-risk population? And so I don't think we need to necessarily extend down into pre-adolescents, at least with initial areas. And then I do think clearly as a vaccine would be developed, we'd be interested in pregnant women and potentially infants and other population groups. That's not the topic for today, but those are different groups for

which you clearly have quite different physiology and issues that would be relevant to your consideration.

In this particular context, I guess I would turn it back to folks who have a better understanding of adolescents and adolescent physiology and the development of the immune system during that period of time. And if the consensus is that we can't identify any meaningful distinctions between a 16-year-old and an 18-year-old, or a 15-year-old and an 18-year-old, and that there's highly unlikely to be any distinctions there, then I might be convinced. But I'd still want to approach that determination with some skepticism in part because of physiology, but also in part because an issue that you had raised early on and that some of the adverse consequences arising out of here might have to do with psychology and maturation from an emotional and behavioral standpoint.

And I think 15-year-olds might well

be different than 18-year-olds in that respect even if they're relevantly similar from a physiological or immunological perspective. And so I'd probably lean heavily on scientific assessment of the immune system during those periods of time to convince me that in fact there were not relevant differences and that we could comfortably extrapolate between those age groups.

DR. FOST: Skip?

DR. NELSON: Just in the interests of clarity, let me ask a question.

Leonard raised the initial question of the degree to which extrapolation may argue that you may not need less in studies. Generally as extrapolation is applied as I went through the definition in the paradigm, it relates to efficacy studies.

The degree to which people are asking whether you need any studies is separate. I don't think that we want to get in -- and in fact we shouldn't -- get into

speculating what kinds of studies FDA would need for licensure.

But what happened is then to Leonard's challenge, others were coming up with reasons with why you might need studies, even if one necessarily could assume you may or may not need efficacy studies. What I'm trying to say is that even if you agree that extrapolation is appropriate, it still leaves open the need for other kinds of studies, and still lays open the question of at the time at which you could initiate that study, what do you need to have in hand to say that initiating that adolescent study, even if it's not for efficacy, would be appropriate.

So I think it is getting us to think about that question, even if we accept that extrapolation is possible. Because it's not. Extrapolation as generally applied is not meant to be used as you don't need any studies.

MR. GLANTZ: Hi. This is Leonard

Glantz.

Extrapolation as it has been used so far is a regulatory term it seems to me. How can you extrapolate for the purposes of regulatory compliance?

I'm really asking and I think as Norm has put it, the question of scientific necessity. That is it's scientific necessary to do studies on this population -- 15, 16, 17-year-olds -- if we know about 18-year-olds.

So we would extrapolate data from 40-year-olds to 20-year-olds. Right? We have these artificial groups based on historical legal policies. There's nothing special about 18 biologically as far as I can tell. What's special about 18 is legal regulatory or whatever.

So I'm really asking the question about scientific necessity of why draw that line, since we don't draw 20- and 40-year-old lines. We regulate things for all adults. And we do that because we assume that there's

some sort of biological consistency.

So I'm just suggesting that we are confusing legal and regulatory things which are arbitrary with scientific questions, which is I think the question that we're asking if it's scientifically necessary to use this group separately.

MS. O'LONERGAN: Terry here. Is it just a matter of determining if we want to use Tanner Staging as a criteria for inclusion? Is that a better physiological -- and could we tie immunological maturity to Tanner Staging? This is a technical question I don't know the answer to. Is that an appropriate way to determine enrollment?

DR. CVETKOVICH: Therese Cvetkovich. I guess one point about that -- and maybe you picked up on the fact that I said postpubertal, which really we use these various ages -- 12, 13, 10. In this country, we've been using 12, and maybe it's not right. But age is usually considered a surrogate for

Tanner Staging or postpubertal.

And it's an excellent discussion to have, but I think the question that would be raised by scientific necessity would be in those adolescents who are postpubertal and therefore considered physiologically to be similar to adults. That's why we think about dosing and treatment with the exception of their ability to provide their own informed consent.

DR. FOST: Jeff?

DR. BOTKIN: Maybe I want to go back to Alan on this question. I'm picking up on Len's comment that we do consider 20- and 40-year-olds perhaps as the same. I'm not sure that that's the case. Doesn't this research in fact subdivide your adult population to look at different aspects of that population perhaps by age or race or country of origin? There are subsets that you would look at to try to make a determination about whether in fact the vaccine was as

effective in one population versus the next even though 20- and 40-year-old may be equivalent from an ethical perspective.

DR. FIX: Just to clarify, is the question in general in our research what age group do we include in adult studies?

DR. BOTKIN: Well, perhaps the question is would it be common to subdivide your adult population to look at relative efficacy in different adult populations and not simply lump all those folks together because they were all adults.

DR. FIX: Yes. And we can do that obviously within our studies. We usually have a fairly wide age group for adults from 18 up through -- well, in discussions with the FDA where we can go could be 45. Sometimes the interest is a little younger. Sometimes it's a little older.

And certainly in say the Step Study, which was in some of the background information, a lot of the post hoc analyses

looked at behavioral issues in younger, older as well. That's certainly a big issue. I think what's being identified here is the importance of not so much perhaps the physiology and the biological response, but is there a behavioral difference between say a 16-year-old and a 19-year-old in the context of a vaccine that is only partially effective? And therefore behavioral inhibition is a huge piece of that balance of whether this vaccine is going to have an important impact.

DR. FOST: Alex?

DR. KON: It sounds as though there's really these two separate issues when we start talking about necessity in adolescents. One is the sort of physiologic difference. And the other is this behavioral difference.

And I guess as I think through it and the question sort of at hand is at this point in this vaccine study, would you include adolescents? And if not, at what point would

you? I guess I would have a hard time thinking about including adolescents at this point because I'm not sure that there's sufficient evidence that there's direct benefit or a prospect of direct benefit.

But I think when we start talking about these psychological issues, we're talking about such a huge variability. A 15-year-old who's in a suburb in Beverly Hills is going to be significantly different than a 15-year-old who's living in the middle of Harlem, for example. And there's going to be huge differences based on socioeconomic status, based on risk behavior status, and access to information.

So I think it becomes very difficult if we're talking about making judgments on the efficacy of this vaccine for adolescents based on these sort of psychological issues to roll that into a study that's this early on when we're talking about a phase 2. So I think when I'm thinking about

whether or not we would be interested in involving adolescents at this point, I think the bigger issue to me becomes is there sufficient evidence at this point that, that population has a real prospect of direct benefit to think about enrolling them at this stage, or is it something that we should put off until later? And I would think I would have a very hard time including adolescents at this stage.

DR. FOST: Can we just hold on to that? I think if we could just bracket that issue, because I think it's a big issue. I just want to stick a little bit more with whether there's a necessity to do it in these separate age groups.

But somebody had their hand up over here.

MS. VINING: Hi. Elaine Vining.

I'm just struck by the fact that the data says that half of the new infections are within the ages of 15 to 24-year-olds. I

don't know if that's considered behaviorally motivated or physiologically motivated. But it's a very telling statistic. And when we're talking about 18-year-olds and whether you can extrapolate to 15-year-olds, I'm also curious, how many 18-year-olds are in these studies? Or are they older individuals and adults, so that we're not really extrapolating from 18-year-olds? We're extrapolating information from 25- or 30-year-olds down to 15-year-olds.

I don't have any sense of where we are with that. But the statistic of half of the new infections being 15- to 24-year-olds I think is significant in this discussion to me.

DR. FOST: Steve?

DR. JOFFE: So a few comments ago, Alex mentioned the HPV vaccine. And I want to raise that in a different context which is that I suspect that many of the issues that we're talking about here came up during discussions about how to do the development of the HPV vaccine.

And I don't that story well enough. I don't know if anybody else at the table does know that story. But the issues of -- that's a vaccine that is now recommended for girls as young as nine. And I don't know the developmental trajectory. What was the role of extrapolation in bringing that to nine-year-olds? Were there studies done in girls as young as nine? How did this conversation go? And thinking through that again, that's a sexually-transmitted disease, so that raised some of the same issues there as an HIV vaccine raises.

So does anybody know that story well enough to sort of tell it and draw out the relevant points for our discussion today?

DR. CVETKOVICH: Hi. Therese Cvetkovich.

I don't know the story well enough except for a very broad brush stroke. And that is there was efficacy in adults before they went into the younger age or teenage

groups. There was clearly the need to target adolescents to prevent that infection during a time when it's most likely to occur.

So the development does have to be based on the epidemiology. But it did not obviate the need to have efficacy in adults first.

DR. FOST: But were there studies of nine-year-olds?

DR. CVETKOVICH: Were nine-year-olds included in the clinical studies? I don't know the answer to that.

DR. FIX: Somebody else may come in here. But I think --

DR. MIDTHUN: Yes. Well, there were safety and immunogenicity data on down to nine years of age. And so the efficacy in terms of actually being able to prevent the clinical disease endpoint was in the older individuals. But there was a lot of safety and immunogenicity data going down to that age.

DR. NELSON: That was Karen Midthun who's the Deputy Director of CBER, just for the record.

DR. FOST: Alan, and then --

DR. FIX: And that actually introduces a fairly important point there, and that's being able to demonstrate meaningful immunogenicity --meaningful in the sense of impact on acquisition and disease. And that's one of the huge constraints we have here.

DR. CVETKOVICH: Right. And so whether you have the ability to correlate efficacy and immunogenicity will really, really determine how you design your studies and what studies can and can't be done.

DR. FOST: Ben and then Skip?

DR. WILFOND: And just for clarification, getting back to the whole issue of licensure, so with the HPV I presume then it is approved for use down to the age of nine? Is that correct?

DR. CVETKOVICH: Down to nine.

DR. FOST: Skip?

DR. CVETKOVICH: I assume that's why the lower age limit came up and what supported that initial cut off.

DR. NELSON: So I'm hearing a fairly strong message that around this issue of scientific necessity that the enrollment of a population -- whether it's an adolescent population or any other population -- ought to be important with respect to a research objective that requires the enrollment of that population. If one wanted to try to state a general ethical principle, there's been different comments about what types of objectives might meet that standard, whether it's objectives of licensure or whether it's looking at behavioral, et cetera.

And my only suggestion is -- I know we have plenty of time so I'm not saying it's a time issue -- but it's also not clear we need to necessarily speculate on what all those research objectives might be that would

meet that ethical standard as opposed to state what we believe that might be. The question then -- once we state that -- still goes back to I think Alex's question. I'm not just saying that. It's just not clear to me we need to necessarily lay out every research objective that might require the enrollment of an adolescent in either this type of vaccine trial or any other type of vaccine trial.

I say that as much to say I hear that as a strong message at a level of ethical principle, and it would be nice to just confirm that in fact that strong message is, in fact, there. Because that alone I believe is helpful.

DR. FOST: I'm not sure I bought into it yet. Or at least it's not clear to me where these boundaries need to be drawn.

So say this hypothetical trial that you mentioned includes 15- to 18-year-olds. And it's shown to be safe and effective. Is it the case that it would be ethically

problematic to give it to a 14.9-year-old? Obviously not. A 14-year-old? I'm not sure why?

Is it the case that the licensure would then restrict it to you have to have reached your 15th birthday? It seems like a very arbitrary distinction. And the same could be said about 18 versus 17.

So I understand the difference between a two-year-old and a 15-year-old. But I don't understand the difference between a 16-year-old and a 17-year-old and that 15 and a 14.

So I'm just saying these boundaries seem to me very arbitrary and not consistent with biology, behavior or anything else.

Ben?

DR. WILFOND: I don't disagree with you, but it occurs to me that even thinking about the HPV vaccine example where you might do studies in 15- to 18-year-olds in terms of the efficacy. But then you might do

additional studies down to the age of nine for example. And then you'd have an approval down to the age of nine. Because clearly you'd want to get that lower range. But the efficacy in the older group would apply to one.

DR. FOST: So you're suggesting at least start with some older adolescents first and see how it goes?

DR. WILFOND: Right.

DR. FOST: That brings us back to Steven's question, which we'll come to in a minute.

So does anyone want to say anymore about -- Skip thinks he's hearing something about something resembling consensus about necessity. I'm not sure I heard it. But -- yes?

DR. NELSON: Let me clarify. There's a level of principle. And then there's issues of scientific judgment about whether or not the biological and

physiological data -- wherever you draw that line. The difficulty there is that's going to be product specific. It'll be different for different drugs. It'll be different for different diseases. Even within vaccines, it could be different.

So I think what I'm saying is not that there's consensus about whether there's any difference between a 13-year-old and 15-year-old in this case. That's not my point. It's the principle that one tries to then apply in the context of one's understanding of the biology and physiology in response, et cetera. That then becomes a very contextualized judgment. I'm not saying there's consensus there. I don't think we necessarily have to come to consensus on that point. Maybe we don't have the right expertise around the table on that precise issue as opposed to the more general principle.

DR. FOST: Jeff, and then Ben and

Len?

DR. BOTKIN: Yes. I would start my line drawing simply around the population at risk. And whoever the kids are who we think need to be protected by this vaccine are the group that we ought to be ultimately testing the vaccine in perhaps through some progression from adults to older kids to younger kids.

But the original line drawing shouldn't be by physiology or by age per se, but should be simply by who it is that needs to be protected from the disease.

DR. FOST: Ben?

DR. WILFOND: Actually my comment really echoes Jeff's last comment. And I want to come back to my recruitment question from the very beginning, but state it in a more positive way.

It occurs to me if our ultimate goal is going to be trying to prevent HIV infection, and if it was a case that at each

year of age there's more and more people who have acquired HIV infection, what are the motivations for designing a study that included people in the 15- to 18-year-old rather than older is that you're more likely to easily find those people and have the answer and information more quickly.

DR. FOST: Len?

DR. BOTKIN: Yes. I actually have a technical biological question, which is has there ever been a drug or a vaccine or a biologic that worked in adults and that was safe and effective in adults that was not safe and effective in 15-, 16-, and 17-year olds?

MR. GLANTZ: Yes.

DR. NELSON: Yes. I don't have the list memorized. No, there are examples. If you do it 17 versus 19, perhaps not. But there's certainly examples of drugs that when they go into testing in pediatrics including adolescents, issues of dosing safety and efficacy are different.

MR. GLANTZ: Than from adults when you're dealing with late adolescents. That's really the question. Because the question that I have is do you need to test it in this population at all if it works on adults, not should it be tested on the population at risk. But if it's fair if you do around 18 and above and we believe it'll be safe and effective in the adolescent population below that, then why do the research on the population?

DR. NELSON: But in answer to your general question have there been differences in other areas, the answer is yes, there have been differences in other areas. So.

DR. MURPHY: Diane Murphy, FDA.

I just wanted to reinforce. We actually now have over 150-some products that we've brought in, in drugs. And we do have discreet differences, particularly in the younger age groups when we get down to 5, 6, 7, 8-year-olds. As someone said, you don't

know what you don't know.

But when you get to the adolescents, we have had a couple of examples where it actually with the dosing particularly may be an issue. Again, this is not vaccines. But with the dosing in those age groups may be different. Some of it may be actually more gender than it is age. So that gets to be an issue. And those are some of those differences that we're seeing.

DR. FOST: Yes. I don't know how common it is, but I'm vaguely remembering one of the anti-epileptics -- it may have been valproic acid -- had more liver toxicity in adolescents than adults. So there are at least some examples.

Alan?

DR. FIX: I just wanted to specify -- clarify -- that the question was raised in the context of vaccines. If that's the case, it's somewhat of a different issue.

DR. FOST: Your answer to that

question?

DR. FIX: That I wouldn't see a difference. We'll hear from the other side.

DR. MIDTHUN: This is Karen Midthun.

I can't offhand think of a vaccine where there has been a difference demonstrated in young adults versus teenagers. But I don't know to what extent that's really been critically looked at in that particular way.

I think as others were saying, clearly we know a lot of differences when you get into the younger age group. But just because I can't think of any offhand doesn't mean that there necessarily aren't.

DR. FOST: Skip, and then Ben?

DR. NELSON: Leonard, having said that, let me admit what I hear as your main message -- which I think is correct -- which is the legal definition of adolescents relative to their capacity to make independent decision-making, which is variable from state

to state as you know obviously, and may depend upon the kinds of decisions that they're considering though usually in this context is the age of 18 that there's no necessary connection between the age of 18 and the biological differences that one might be discussing in any given product area when you look at say 17 versus 19, et cetera. So that if in fact the legal definition in the United States -- which it is not -- was 16, now whether that's a closer relationship between biology and the judicial and legal system could be a point of debate.

I think from that standpoint arguing for that potential disconnect and pointing that out I think is true. Saying and then carrying that into the area of saying of what's then necessary as you go from 18 down becomes a much more context-specific discussion.

So I think yes, there's some examples either way. But if you wanted to

press well how many 17-year-olds there were versus 14-year-olds, I think that would begin to sort of try to cut the data in a much too fine a point. So your general point I think is well taken.

DR. FOST: Ben, and then over here.

DR. WILFOND: I have a question that's really motivated by Leonard's comments. And I have a question for you to respond to, which has to do with whether your sense is that research is something all things being equal we should avoid doing kids unless we have to, or one that we actually ought to be encouraging. I'm going to explain why I'm asking a question.

It occurs to me that if we were able to gather the data in adults and then therefore extrapolate to kids -- and not to the researching kids, but just have it available and do it to kids -- is that better or worse than actually first having that data in adults and then before we release it to all

kids, we do a study in kids because that way we actually can learn a little more and protect those first people who get the vaccine in the context of research rather than doing it in clinical practice where all bets are off and there's probably much more risk involved than having it as part of a research study.

MR. GLANTZ: Yes, usually I prefer to ask questions and answer them.

But what I would say is that all things being equal, it's better not to do research in kids if you don't need to -- if there's no scientific necessity. And that's why I'm really trying to ask the scientific necessity question that if we can answer the question about the efficacy and safety in kids without using kids, why use them.

DR. WILFOND: It would seem to be that part of the response to that might be because it's safer for the children when they're first exposed to that new product to do it in the context of research rather than

doing it in the context of clinical practice.

DR. FOST: I would add to that, that the reality is that all drugs get used off-label whether they ought to be or not, and marketed, I might add indirectly. And so, they're going to be used in kids. And the examples are too numerous to count in which we learn decades later. Oxygen was fine for 20-year-olds, but not so good for preemies, and lots of other examples in between.

MR. GLANTZ: I don't dispute that at all. And again, I'm not talking about five-year-olds or two-year-olds. I'm talking about adolescents. I'm talking about late adolescents. And that's why I'm asking a scientific necessity question about how different are they.

So if we didn't have any laws at all about this -- right -- any laws at all -- I would be surprised if a scientist would say let's draw the line at 18.

DR. FOST: Jeff?

DR. ROSENTHAL: Jeff Rosenthal.

I think this discussion on scientific necessity and how it influences the studies is really interesting. But for me, the other dynamic is that the risk spectrum really seems to change. And so how does the risk/benefit for a study participant -- how is that influenced by the age of the subject?

So as we're considering the ethical conduct of research in this group, one element to keep in mind is that the scale isn't even across any of these groups. It's changing. And I'm having a hard time getting my arm around that issue. We haven't really started to tackle that so much. But that's what the issue is for me.

DR. FOST: Okay. I'm going to suggest moving ahead. It was Alex that raised it, not Steve as I said earlier to sort of the next version of this question of whether to include adolescents or not. As I understand Alex's question about -- Alex asked whether

there's a reasonable prospect of direct benefit. In this particular case, is it sufficient using adolescents at all? And let me amplify that query and then get some reaction to it.

The history here is dismal. In however many years of AIDS vaccine -- HIV vaccines -- nothing very good has happened, and some bad things have happened with the Step Trial. And Dr. Fauci and others said he's not sure anything good is ever going to happen, and it may be at best a decade before we have anything that's really useful.

You never know for sure, and it's not a reason to give up by a long shot because it's so important an issue. But is the weight of the evidence such that this particular trial is so unlikely to be of benefit right now to adolescents that it's really stretching it to say there's a reasonable prospect of benefit and that that's a reason for just let the competent adults decides -- the ones who

can consent -- and see what happens.

So let's have a discussion about reasonable prospect of direct benefit.

Alan?

DR. FIX: Well, I'm not quite sure I'm going to be addressing the way you've phrased it. But I think the question is why at this stage of testing of a product you'd bring adolescents in, when this study is being proposed as a proof-of-concept phase 2 -- or call it phase 2b -- is not intended to take a product a licensure. Therefore, not including adolescents at this point, even if you were trying to shoot for an indication on approval, wouldn't be crucial. They could be brought in at a later stage in a full phase 3 study that would be intended to lead to licensure.

I will say that looking back a bit for a step and the companion study that was performed in South Africa, there were a lot of discussions about what happens if it hits a home run in the phase 2b study. Could it

potentially be used for licensure? And that was hugely speculative. And on the basis of that, there were considerations of trying to bring adolescents into some of those studies which we did not do.

But the whole outcome of Step as well, with the introduction of safety issues that arose only in the context of an efficacy study, and were not anticipated out of all of the phase 1 and phase 2a studies, I think it's changed the thinking of a lot of people who were pushing a little more aggressively to have adolescents involved in this kind of study in the past.

DR. FOST: Other comments? Ben?

DR. WILFOND: Well, I think your question about prospect of direct benefit is an important one. And there's at least two different ways that I've heard people try to interpret this.

One is one in which it's impossible for there to be a prospect of direct benefit

because of the design of the trial. Even if the drug actually worked, it still wouldn't benefit the person because either they're giving too low a dose or because they're only giving one dose and the disease requires multiple doses.

But the second version is one in which -- as you described this -- really unlikely to work, but in fact if it did work, then there would be benefit to that person. I think that's often the experience in phase 1 oncology trials. And I'm curious at Steve's reaction to this because I know some oncologists would categorize phase 1 oncology research as a prospect of direct benefit because even though the chance is really, really low, if it worked it would be good.

DR. JOFFE: I think that's right. And that's a good analogy. And I suspect that if you look at most IRB approvals of phase 1 oncology trials, they would be approved under the prospect of direct benefit section of the

regulations. I'm fairly convinced that is the case.

And you're absolutely right, Ben, that there are arguments and literature about whether that's fair to do. But I think that, that's the way the world has gone.

The question of whether -- just to sort of think about it -- the term "reasonable prospect of direct benefit" has been used here. And actually, I'm not trying to do sort of textual regulatory analysis with this comment or semantics or anything like that. But I think the structure of the reasoning about this -- the first question is, is there a prospect of direct benefit. And then the reasonable part comes in when we start to think about the relationship between that prospect of direct benefit and the risks.

And so I was just looking back at the language of the regulations. And we're talking about 52 clinical investigations involving greater than minimal risk but

presenting the prospect of direct benefit to individual subjects. So there's no qualifier in that section on prospect of direct benefit. And so I feel fairly comfortable saying yes, there is a prospect of direct benefit, assuming you don't push me for qualifiers.

Where it gets challenging is then seeing whether the additional criteria are met. So is the risk of being a participant in this hypothetical study justified by the anticipated benefits to subjects? That I think is a really hard question to answer. And is the relation of the anticipated benefit to that risk at least as favorable to the subjects as that presented by available alternative approaches? That's a really hard question to answer.

I think the question is there a prospect of direct benefit is actually not such a hard question to answer because I can't rule it out. It may be like some phase 1 oncology studies in the sense that it's very

low. But it's hard to rule out completely. But that doesn't mean that we can go ahead and do it because we still have to meet these additional considerations which I think are going to be the challenging ones.

DR. FOST: Jeff, and then Alan?

DR. BOTKIN: I wanted to get back to Norm's comment just to say that I do think the track record in this domain is quite relevant to your assessment in that regard, and that with multiple vaccine trials having failed, I think is quite relevant to basically a determination about the prospect of development for any new agent that comes along unless there's something fundamentally different about that.

But, I would also say in that same vein that we need to be careful about the prospects of a false negative, which is to say if you demonstrate that it's not working in adults, then you assume it's not going to work adolescents. And in fact there might be

relevant differences in those populations, and you'd be foregoing the possibility of benefits to kids by having a negative trial in adults.

And obviously understanding why the trial was negative in adults, and if there's something about adolescents that makes them relevantly different, then conceivably you could test a vaccine in adolescents even though it had failed in adults if you have a strong enough rationale about the difference in those populations.

DR. FIX: I just come back to Steven's definition of direct benefit and well defined it is. I think this study would better define that prospect of direct benefit for the subsequent study. And I think that would be the more important consideration, as well as for the defining any safety risks in that balance.

DR. FOST: So as I understood your comment, Steve, technically if an IRB were going to approve it, that's the category in

which it would be approved because it's not a "non-therapeutic study." It's obviously intended. But that begs the question of whether the facts are sufficient to go ahead with it, whether the reasonable, the plausible prospects of benefit are really sufficient here to justify what might be significant risk.

DR. JOFFE: So I'd be fairly comfortable saying that there was a prospect of direct benefit. But then when forced to address the next consideration, which is that the risk of being a participant in the study justified by that prospect of direct benefit, to which I would believe to be very small based upon the very limited information that we have at this moment. I would be challenged to answer that question, yes, because I believe that the risks of participation in the study are significant and substantial. And so I'm not sure I would be able to say those risks are justified by that prospect of direct

benefit given how very small it is likely to be given the great deal of uncertainty that there is likely to be around it at this point.

Perhaps with the proof-of-concept study in adults, if the efficacy data were looking promising, then we could begin to answer that question more affirmatively in follow-on research.

DR. FOST: Skip?

DR. NELSON: I just want to make sure I'm hearing you correctly, Steve.

What I hear you saying is to reach the threshold of prospect of direct benefit alone, independent of the other language that's in 50.52, that you don't need any data to support that. That's effectively what I hear you saying.

DR. JOFFE: I'm not sure I'd go quite that far. But I don't think that you need efficacy data from other settings -- from other human clinical settings.

So for example, with primate

models, could one take primate models suggesting immunogenicity and effectiveness at preventing disease or reducing the severity of disease based on primate models and say from that, that when we take this to the first human subject whether adult or pediatric -- who's ever going to get the analogous human vaccine -- that there is a prospect of direct benefit there. And I think one could extrapolate from the pre-clinical models to say yes, there is a prospect of direct benefit from that very first human subject -- again, adult or pediatric -- who is going to be getting that drug or that vaccine, but with a great deal of uncertainty, and based upon the historical track record here, a very low likelihood.

And so it's not so difficult for me to make that extrapolation to answer the question of prospect of direct benefit affirmatively based -- not upon no data, but no human clinical data. It is much more

difficult to then say if the risks are substantial, how can we use that to justify the risks.

DR. FOST: Ben is poised.

DR. WILFOND: I just wanted to add to Steve's comment when he was speaking. It reminded me that in terms of talking with oncologists, and the last few years I've heard them throw out the term phase 0 trials, which refer to those trials in which there's absolutely no chance it'll work. So their threshold for calling it phase 1 is just that maybe it might do something possibly.

DR. FOST: Skip?

DR. NELSON: I'll just point out the case for tomorrow morning is selected to sort of explore to some extent the issue of inferring prospect of direct benefit in the absence of any other data besides animal data.

And part of the background in this instance is -- it's my understanding at least -- that those kinds of models in this setting

are deficient, I guess would be the best way to put it. So even if you put efficacy aside, you don't have the standards thing. You have to prove efficacy, which was part of the reason for asking you to think about the distinction between efficacy and direct benefit.

It still then leaves open the question of the threshold of evidence that you need to say there's a sufficient prospect of direct benefit to move into pediatric trials.

DR. FOST: Jeff?

DR. BOTKIN: So let me see if I understand what you're saying, Steve.

It's that in this context with this described trial that 405 or 52 is the right category to be considering it. So we've